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(71) Applicant *(for all designated States except US)*: CLOVER CONSOLIDATED, LIMITED [CH/CH]; 37, avenue de Rumini, CH-1002 Lausanne (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : DESAI, Neil, P. [IN/US]; 847 Alandale Avenue, Los Angeles, CA 90036 (US). SOON-SHIONG, Patrick [US/US]; 12307 Dorothy Street, Los Angeles, CA 90049 (US). SANDFORD, Paul, A. [US/US]; 2822 Overland Avenue, Los Angeles, CA 90064 (US).

(74) Agent: REITER, Stephen, E.; Pretty, Schroeder, Brueggemann & Clark, 444 South Flower Street, Suite 2000, Los Angeles, CA 90071 (US).

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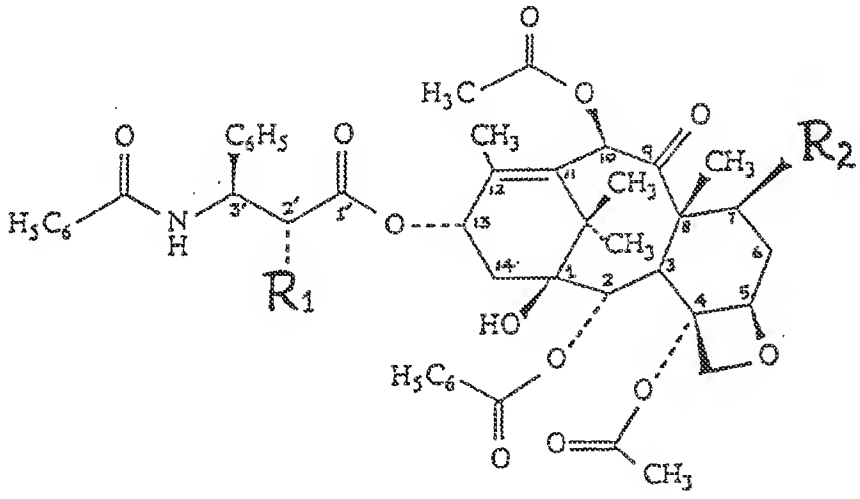

(57) Abstract

In accordance with the present invention, there are provided polymeric drug delivery systems in which the drug is bound to a water-soluble polymer to provide a form of soluble drug delivery especially for those cases in which the drug by itself is water-insoluble. In particular, the drug taxol is covalently bound to water-soluble polyethylene glycols such as linear polyethylene glycols, branched polyethylene glycols, star polyethylene glycols, and branched copolymers of polyethylene glycols with other functional monomers to comprise a form of polymeric drug delivery. Also, cross-linked insoluble gels of these materials are prepared to serve as a form of implantable drug delivery.

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WATER-SOLUBLE POLYMERIC CARRIERS FOR DRUG DELIVERY

FIELD OF THE INVENTION

The present invention relates to the drug delivery of taxol wherein the drug is chemically bound to a water-soluble polymeric or macromolecular carrier that renders the drug water-soluble. In another aspect, the present invention relates to water-soluble prodrugs of taxol that recover their biological activity when hydrolyzed from the carrier molecule. In a further aspect, the present invention relates to sustained drug delivery of taxol by hydrolysis from an implanted gel comprising the drug-carrier conjugate.

BACKGROUND OF THE INVENTION

Taxol is a natural product first isolated from the Pacific Yew tree, *Taxus brevifolia*, by Wani et al. (1971, *J. Am. Chem. Soc.* 93:2325). Among the antimitotic agents, taxol, which contains a diterpene carbon skeleton, exhibits a unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. In contrast with other antimitotic agents such as vinblastine or colchicine, which prevent the assembly of tubulin, taxol is the only plant product known to inhibit the depolymerization process of tubulin. This prevents the cell replication process and taxol has been shown to have significant antineoplastic and anticancer effects in drug-refractory ovarian cancer. Taxol has shown excellent antitumor activity in a wide variety of tumor models such as the B16 melanoma, L1210 leukemias, MX-1 mammary tumors, and CX-1 colon tumor xenografts. Several recent press releases have termed taxol as the new anticancer wonder-drug. The poor aqueous solubility of taxol has, however, remained a setback in human clinical trials, and currently used formulations require a cremaphore to solubilize the drug. The human clinical dose range is 200-500 mg and

requires about one liter of fluid given intravenously using the cremaphore. In phase I clinical trials taxol itself did not show excessive toxic effects but severe allergic reactions were caused by the emulsifiers administered to solubilize the drug.

The general chemical structure of taxol is shown in **Figure 1** in which $R_1 = R_2 = OH$. Potential sites for modification of the drug are at the hydroxyls on the 1, 7, and 2' carbon atoms. The 1-hydroxyl is sterically hindered and nonreactive, the 2'-hydroxyl is the most reactive, followed by the 7-hydroxyl which is also sterically hindered. Thus the modification of taxol to increase its water-solubility has revolved around the modification of the 2'- and the 7-hydroxyls. Studies have reported that the C-13 ester side chain and the 2'-hydroxyl group on the side chain are essential for biological activity. Mellado et al. (1984; *Biochem. Biophys. Res. Commun.* **124**:329-336) have reported the synthesis of 2'-acetyl, 7-acetyl, and 2',7-diacetyl taxol. An acetyl at the 2' position resulted in a loss in ability to promote microtubule assembly. Taxol and 7-acetyl taxol were similar in their ability to alter cell proliferation and microtubule polymerization. These observations suggest that the 2'- and 7-positions are suitable for structural modifications, the 2'-position as a site for reversible derivatization (or formation of a prodrug) and the 7-position for analogue/prodrug modifications.

A number of chemically modified taxols with enhanced water-solubilities have been developed. Among them are the sulfonated derivatives (Kingston et al., 1991, US Patent 5,059,699), and amino acid esters (Mathew et al., 1992; *J. Med. Chem.* **35**:145-151) Which show significant biological activity. However, the delivery of taxol attached to a macromolecular or polymeric water-soluble carrier has not been considered. Nathan et al. (1990;

Polymer Preprints 31:213-214) have described a polyethylene glycol (PEG) chain-extended with amino acids such as lysine, to produce a polymer which has pendant carboxylic acid groups that may be used to attach biologically active molecules. However, no mention is made of the immobilization of taxol, or the attachment of a water-insoluble drug to such a carrier in order to deliver it in a soluble form.

In the present invention, to deliver taxol in a water-soluble form we have used a water-soluble polymer to which the drug is bound, the resultant polymer-drug conjugate being soluble. Water-soluble polymers such as PEG, have been investigated extensively in recent years for use as nontoxic, biocompatible, protein repulsive, noninflammatory, and nonimmunogenic modifiers for drugs, proteins, enzymes, and surfaces of implanted materials. These characteristics have been variously attributed to a combination of properties of these polymers, e.g., nonionic character, water solubility, backbone flexibility, and volume exclusion effect in solution or when immobilized at a surface. The solubility of PEG in water as well as a number of common organic solvents facilitates its modification by a variety of chemical reactions and makes it amenable for binding water-insoluble or poorly water-soluble molecules and rendering them water-soluble.

The preparation of a reversible PEG-taxol derivative at the 2'- and/or 7-position on taxol serves as useful aqueous-soluble prodrug. A nonreversible PEG derivative on the 7-position of taxol serves as a useful water-soluble drug analogue.

Advantages of delivering the drug attached to a water-soluble polymer as described in the present invention are many fold. The number of drug molecules per polymer molecule can be controlled; the circulation time of the

drug can be varied by adjusting a number of variables including molecular weight of the polymeric carrier, the type of linkage between the drug and polymer, i.e., some linkages are hydrolyzed at much faster rates than others; large increases or decreases in blood levels of the drug may be avoided in favor of more gradual and sustained levels obtained by continuous release of the drug from a polymeric carrier; and the hydrolysis of the drug-polymer conjugate results in the formation of the original biologically active drug and the innocuous water-soluble polymer that is excreted from the body.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method of drug delivery that utilizes water-soluble polymers as carriers for a drug. The delivery of drugs that are inherently insoluble or poorly soluble in an aqueous medium can be seriously impaired if the only suitable mode of delivery is by intravenous injection. The attachment of such drugs to water-soluble macromolecules that act as carriers can greatly benefit this problem and allow for intravenous, subcutaneous, or intramuscular delivery. Examples of poorly aqueous drugs that may benefit from this form of drug delivery are taxol, amphotericin B, etc. Examples of water-soluble polymers that may be used as carriers in such a system are polyethylene glycols (PEG), polyvinyl alcohol, polyhydroxyethyl methacrylate, polyacrylamide, polyacrylic acid, polyethyloxazoline, polyvinyl pyrrolidinone, and polysaccharides such as chitosan, alginates, hyaluronic acid, dextrans, etc.

In a preferred embodiment, the drug to be delivered is taxol, a naturally occurring diterpenoid which has been described as a potent antineoplastic and anticancer agent, and the polymeric water-soluble carrier is polyethylene glycol and derivatives thereof.

In another preferred embodiment, taxol is covalently linked to a PEG carboxylic acid derivative by an esterification at the 2'-position on the taxol side chain.

Another preferred embodiment involves the esterification of taxol at the 2' position with succinic anhydride or glutaric anhydride followed by esterification with PEG to obtain the PEG-taxol derivative.

In yet another preferred embodiment, a multi-arm 'star' or 'branched' PEG is used as the carrier to increase the loading (number of drug molecules per carrier molecule) of taxol on the PEG.

In another preferred embodiment, an acrylate derivative of PEG is copolymerized with acrylic acid to obtain a copolymer with a multiplicity of carboxyl functionalities that are sites for the attachment for taxol.

Another embodiment of the present invention is to covalently attach taxol to a PEG-amine derivative by first reacting taxol with carbonyldiimidazole followed by reaction with PEG-amine to obtain a urethane linkage. This link is not readily hydrolyzable and such a derivative at the 2'-position interferes with the biological activity of taxol. It is therefore an embodiment of the present invention to produce such a PEG derivative at the 7-position of taxol which retains its biological activity.

In another embodiment, the drug may be linked to a star or branched PEG in which a part of the endgroups of the PEG have been covalently linked to the drug while the remainder are covalently linked to an unsaturated group such as the acrylate group that may be polymerized in a free radical process to obtain a crosslinked polymer. The resultant crosslinked polymer, absorbs water in aqueous

medium and results in the formation of a hydrogel containing bound drug. This hydrogel may be implanted in a suitable location subcutaneously or intraperitoneally for sustained release of the drug by hydrolysis from the insoluble crosslinked carrier.

Thus it is a primary object of this invention to produce a derivative of taxol on a water-soluble macromolecule or polymer as a carrier that can be used for delivery of taxol in a soluble form.

It is a further object of the present invention to use a hydrolyzable linking group such as an ester to allow for the hydrolysis of the drug-polymer conjugate subsequent to delivery of the drug to form the original active drug and polymeric carrier.

It is yet another object of the invention that the drug produced upon hydrolysis retain its original biological activity and also the nonhydrolyzable derivative of the drug maintain its biological activity.

It is still a further object of the present invention to simplify the purification of the water-soluble conjugate by utilizing a polymeric carrier such as PEG that can be isolated by a simple precipitation.

DESCRIPTION OF THE DRAWINGS

Figure 1 is a general chemical structure for derivatives of Taxol where R_1 and R_2 are the sites of derivatization. The structure represents the unmodified Taxol molecule when $R_1 = R_2 = OH$.

DETAILED DESCRIPTION OF THE INVENTION

Water-soluble polymers such as PEG (Aldrich), and monomethoxy PEG (MPEG, Nippon Oil and Fats) were utilized to bind poorly aqueous-soluble drugs. Taxol (Sigma chemical) was the drug utilized for covalent linking to the carrier polymers. The 8-arm 'star' PEG polymer (MW 22800) was obtained from Macrochem Labs and acrylic acid from Aldrich. It should be recognized by anyone skilled in the art that other water-soluble polymers and other drugs may be utilized in a similar form of drug delivery. Examples of water-soluble polymers (denoted hereon by P) that can be used as carriers in such a drug delivery system are polyethylene glycols (PEG), polyvinyl alcohol, polyhydroxyethyl methacrylate, polyacrylamide, polyacrylic acid, polyethyloxazoline, polyvinyl pyrrolidinone, and polysaccharides such as chitosan, alginates, hyaluronic acid, dextrans, etc. These polymers can be covalently linked to the drugs by means of linkages (denoted hereon by X) such as ester, diester, urethane, amide, secondary or tertiary amine, ether etc.

The purpose of covalently linking a water-insoluble or poorly water-soluble drug (denoted hereon by D) to a water-soluble polymer is to solubilize the drug in water to enable its delivery in a soluble form into the body. The solubility of taxol in water is very low, approximately 0.03 mg/ml, and at the required dosage of 200-500 mg, this requires the infusion of a liter of fluid using a cremaphore to solubilize the drug. Thus it is desired to improve the solubility of taxol by conjugating it with a water-soluble polymer.

With reference to **Figure 1**, **Table I** below shows the chemical formulas of derivatives of taxol with linear PEGs and some intermediates used in the preparation of these derivatives. The R_1 and R_2 substituents on taxol vary

according to derivative and are indicated by the compound numbers which are used throughout the specification. Taxol itself is represented by **compound 1**.

Table I

Compound Number	R_1 (2'-position)	R_2 (7-position)
1	OH	OH
2	$OCCOC_3H_3N_2$	$OCOC_3H_3N_2$
3	$OCONH(CH_2CH_2O)_nCH_3$	$OCONH(CH_2CH_2)_nCH_3$
4	$OCOOCH_2CCl_3$	OH
5	$OCOOCH_2CCl_3$	$OCONH(CH_2CH_2O)_nCH_3$
6	OH	$OCONH(CH_2CH_2O)_nCH_3$
7	$OOC(CH_2)_2COO(CH_2CH_2O)_nCH_3$	OH
8	$OOC(CH_2)_2COOH$	OH
9	$OOC(CH_2)_3COOH$	OH
10	$OOC(CH_2)_2COO(CH_2CH_2O)_nCH_3$	OH
11	$OOC(CH_2)_3COO(CH_2CH_2O)_nCH_3$	OH

n is the degree of polymerization or number of repeat units in the polymer chain and is dependant on the molecular weight of the polymer.

Table II below shows the general chemical formulas of linear PEG and its derivatives and intermediates utilized to obtain the drug-PEG conjugates. The general formula for PEG and derivatives is $R_3(CH_2CH_2O)_nCH_2CH_2R_4$ in which the flanking groups R_3 and R_4 vary according to the derivative. PEG itself is represented by **compound 12** in which $R_3 = R_4 = OH$. Thus a 'linear bifunctional' PEG is represented by the compound **12** having two hydroxyl groups available for chemical reaction while a 'linear monofunctional' PEG is represented by compound **13** in which one end of the PEG is 'capped' with a nonreactive alkoxy or aryloxy group.

Table II

Compound	Abbreviation	R_3	R_4
12	PEG	HO	OH
13	MPEG	CH_3O	OH
14	MPEG-amine	CH_3O	NH_2
15	MPEG-COOH	CH_3O	$OCO(CH_2)_2COOH$
16	PEG-monoacrylate	HO	$OCOCH=CH_2$
17	PEG-monomethacrylate	HO	$OCOC(CH_3)=CH_2$
18	MPEG-acrylate	CH_3O	$OCOCH=CH_2$
19	MPEG-methacrylate	CH_3O	$OCOC(CH_3)=CH_2$

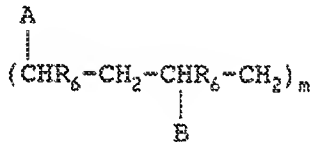
The derivative of taxol having PEG at the 2' and 7 positions (compound 3) was prepared by first reacting taxol with 1,1-carbonyldiimadazole (CDI) as a coupling agent and subsequently with monomethoxy polyethylene glycol-amine (MPEG-amine, 14) to obtain the PEG derivative coupled by a urethane linkage which is relatively stable to hydrolysis. This derivative was not expected to have a high biological activity since the 2' position on taxol was substituted. In order to prepare a 7-PEG derivative of taxol, the 2' position was first protected with the [(2,2,2-trichloroethyl)oxy]carbonyl, or 'troc' protective group by reaction of taxol with 2,2,2-trichloroethyl chloroformate. The 2' protected derivative was then reacted with CDI and MPEG-amine as above to obtain the 2'-troc-7-PEG derivative followed by removal of the troc group to obtain the 7-PEG taxol. The water-solubility of these derivatives was determined in a UV spectrophotometer which clearly showed an absorbance for taxol when coupled to PEG. A wide range of MPEG-amine molecular weights, as well as other linear PEGs used for coupling of drugs can be utilized. Typically a molecular weight range of 200-100000 (corresponding n values between 5-2500) could be utilized for the derivatization. A preferred range is 600-20000 (n = 10-500) and the most preferred range is 1000-10000 (n =

20-250).

Another approach used was to deliver taxol in a soluble form such as the PEG derivative that could be hydrolyzed to release taxol in an active form after delivery of the drug-polymer conjugate. In this method taxol was linked to PEG at the 2' position by a readily hydrolyzable ester linkage. Two approaches were adopted to synthesize this derivative. The first involved modifying the hydroxyl end groups of MPEG with succinic anhydride to obtain the succinyl derivative of MPEG **(15)**. This derivative was esterified with the 2'-hydroxyl on taxol using dicyclohexyl carbodiimide (DCC) and 4-dimethylamino pyridine (DMAP) to obtain the derivative **7**. The second approach involved modification of the 2' hydroxyl on taxol with succinic or glutaric anhydride to obtain the succinyl **(8)** or glutaryl **(9)** derivative of taxol which was esterified with the MPEG hydroxyl using DCC and DMAP as before. Both these procedures resulted in the formation of 2'-MPEG taxol **(10 or 11)** that was readily hydrolyzable in an aqueous environment to give back active taxol and water-soluble carrier. A monofunctional PEG (MPEG) or a bifunctional PEG (regular PEG) could be used for this reaction. PEG (MPEG and/or PEG) molecular weights 200-100000 (n = 5-2500) could be utilized for the derivatization. A preferred range is 600-20000 (n = 10-500) and the most preferred range is 1000-10000 (n = 20-250).

In the above functionalization techniques, the number of drug molecules per carrier molecule is restricted to a maximum of two taxol molecules per molecule of PEG, and only one taxol per MPEG. In order to increase the number of taxols per carrier molecule, PEGs with multiple arms such as branched molecules or star molecules are used. A branched PEG was produced by solution polymerization of the monoacrylate derivative **(16)** or monomethacrylate

derivative (17) of PEG-2000 in the presence of the thermal free radical initiator, 2,2'-azobisisobutyronitrile (AIBN). Thus the number of available sites for coupling the drug to the 'brush-like' polymer was dependant on the number of PEGs having a free hydroxyl group that were incorporated into the growing polymer chain during the polymerization process. Any one of the reactions mentioned above for linear PEGs could be utilized to covalently link molecules of taxol to the branched polymer. Also, mixtures of PEG-monoacrylates of differing molecular weights could be utilized for the synthesis of a brush-like polymer in which the 'bristles' are of differing lengths. The general formula of branched PEGs synthesized for subsequent drug attachment is shown below:



wherein A = R_5 $(CH_2CH_2O)_nCH_2CH_2OCO$, and R_5 = HO (in case of PEG) or CH_3O (in case of MPEG);

wherein B = R_5 $(CH_2CH_2O)_pCH_2CH_2OCO$, and R_5 = HO (in case of PEG);

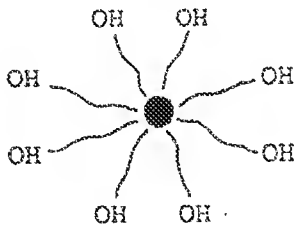
wherein R_6 = H or CH_3;

wherein m, n, and p are the degrees of polymerization or number of repeat units in the polymer chain and are dependant on the molecular weight of the polymer. Typically m, n, and p = 5-2500.

When a drug D is bound to the above polymer through a covalent linking group X, the general formula remains the same except for R_5 which is replaced by D-X-.

'Star' molecules of PEG available commercially, e.g., 8-arm PEG, MW 22800, were functionalized with taxol using the techniques described above. These molecules may have a 'central core' of divinyl benzene (DVB) which is

anionically polymerized under controlled conditions to form living poly DVB nuclei having a predetermined number of active sites to which ethylene oxide is added to produce a known number of arms of PEG and quenched with water when the desired molecular weight is achieved. Alternately, they may have an oligomeric glycerol central core that is ethoxylated and used to initiate polymerization of ethylene oxide and quenched with water when the desired molecular weight is achieved. The range of usable molecular weights of these polymers ranges between 5000 and 200000 with a preferred range of 10000-100000 and a most preferred range of 20000-70000. The upper limit of this latter range is necessary for the carrier to be excreted from the circulatory system. A general formula for the star PEG is $[HO\text{-}(CH_2CH_2O)_nCH_2CH_2]_q\text{-}$(central core) in which q is the number of arms of PEG attached to the central core. When a drug D is bound to the star polymer through a covalent linking group X, the general formula remains the same except for HO- which is replaced by D-X-. The number of arms, q can vary between 2 and 100. A schematic of a star PEG molecule with 8 arms (q = 8) is shown below:

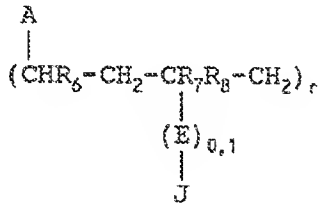


wherein ~~~~ = arms of PEG

and ● = central core

A modified version of the branched polymer system also used as a drug carrier was synthesized by copolymerization of a PEG or MPEG monoacrylate with

'functional monomers'. Functional monomers are defined as those monomers that bear reactive functional groups that can be utilized for coupling of drugs. Examples of these are acrylic acid to provide carboxylic acid groups, allyl amine to provide primary amine groups, allyl alcohol to provide additional hydroxyl groups, or allyl chloride to provide chloride groups attached to the backbone of the branched copolymer. The copolymerization of acrylic acid and MPEG-5000 monoacrylate was carried out in toluene in the presence of the thermal free radical initiator, 2,2'-azobisisobutyronitrile (AIBN). Nonlimiting examples of functional monomers used in the synthesis are those bearing the carboxyl group, e.g., acrylic acid, vinyl acetic acid (3-butenoic acid) and higher homologues; those bearing the amine group, e.g., allyl amine and higher homologues; those bearing the hydroxyl group, e.g., allyl alcohol (2-propene-1-ol) and higher homologues; allyl chloride (3-chloropropene), other unsaturated halides and corresponding higher homologues. The presence of these pendant functional groups allows for the attachment of a wide range of drugs possessing different functionalities. The general formula of copolymers of PEG and functional monomers synthesized for subsequent drug attachment is shown below:



wherein A = $R_5(CH_2CH_2O)_nCH_2CH_2OCO$ and R_5 = HO (for PEG) or CH_3O (for MPEG);

wherein R_6 = H or CH_3;

wherein R_7,R_8 = H, CH_3, alkyl, or aryl;

wherein E = optionally alkyl or aryl;

wherein n and 4 are degrees of polymerization and vary between 5 and 2500;

and J = COOH, OH, CHO, NH_2, Cl, Br, or I.

When a drug D is bound to the above polymer at the site J, through a covalent linking group W (selected from the same groups as X, but not necessarily identical), J is replaced by D-W-. Also the drug may be bound at A, in which case R_5 is replaced by D-X-.

The above text describes the production of taxol derivatives with water-soluble polymers. These soluble polymeric carriers containing the bound drug may be crosslinked to produce an insoluble polymer matrix which is water-swellable and has hydrogel properties. Such a matrix may be prepared in the form of a sphere, disc, cylinder, etc. that could be subsequently implanted at a suitable site for sustained release of the bound drug by hydrolysis. Such a matrix is prepared by utilizing a branched or star PEG in which a portion of the available sites are functionalized by polymerizable acrylate or methacrylate groups and the remainder are bound to the drug. This polymer is isolated, dissolved in aqueous buffer (or organic solvent) and crosslinked by a free radical process that may be thermally initiated or photoinitiated. Following crosslinking, the gel is desiccated by drying in vacuum and stored dry until before use when it is hydrated. To carry out the crosslinking step in organic solvent, the polymer is dissolved at a suitable concentration to obtain a solution of mild viscosity, a thermal initiator such as AIBN, or a UV photoinitiator such as 2,2-dimethoxy-2-phenyl acetophenone (DMPA) is added. To prepare the gel in the form of a disk, the solution is poured into a mould and heated or exposed to long wave UV radiation to crosslink the polymer. If the crosslinking step is to be carried out in aqueous medium, the same procedure is followed except for replacing the organic solvent with an aqueous buffer, adding a water-soluble UV initiator such as 2,2'-azobis-(2-amidinopropane)hydrochloride (AAPH) and exposing to UV